IDP can exploit these two different types of flexibilities to optimize their signaling function.

2440-Pos Board B132
The Impact of Molecular Dynamics Methods on the Accuracy of Simulations of the Disordered Protein Sic1
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Intrinsically disordered proteins (IDPs), proteins that lack a uniquely folded structure, comprise a significant portion of eukaryotic proteomes and play essential roles in signal transduction and cell cycle control. Mapping the dynamics and conformational ensembles of these proteins is essential to understanding their function. IDPs are generally thought to bind via coupled folding and binding. Sic1, however, even in its bound state with Cdc4, remains largely disordered and 'ultrasensitive'. The lack of static structure and dynamic nature of this process poses challenges for many traditional biophysical techniques, highlighting the importance of computational methods for its characterization. Molecular dynamics (MD) simulations of IDPs are often complicated by biases introduced by force fields originally optimized to simulate folded proteins. Often simulations oversample secondary structure and lead to collapsed protein conformations. This study aims to consider canonical MD force fields and simulation methods and how accurately these techniques are able to reproduce experimental results. We carried out simulations in both implicit and explicit (with varying salt concentration) solvents with the force fields Amber12, Charmm27, OPLS-AA and Gromos at multiple temperatures. Simulations in implicit solvent were not able to recapitulate experimental structural data and always led to collapsed structures. Simulations in explicit solvents (TIP3P, TIP4P and SPC water models were used where appropriate for force field) achieved more native-like states, however some still led to collapse. Salt concentration had a strong impact on the compactness of the protein providing clues into the source of non-native compactness in MD simulations of IDPs.

2441-Pos Board B133
Role of Intrinsic Helicity Within N-Terminal Flanking Sequences on Huntingtin Aggregation Mechanisms
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Huntington's disease (HD) is associated with CAG repeats within exon 1 that lead to polyglutamine (polyQ) expansions in the protein huntingtin (htt). Aberrant splicing of htt transcripts generates N-terminal fragments in a polyQ length dependent manner that span exon 1 of htt. These N-terminal fragments can be trafficked into the nucleus and form neuronal nuclear inclusions. Within exon 1 of htt the polyQ region is flanked by a N-terminal 17-residue amphipathic stretch (N17) and a C-terminal proline-rich stretch. Modulation of these flanking sequences has profound effects on HD progression. Specifically, post-translational modifications and single / double point mutations within N17 can modulate the intrinsic helicity of N17, as well as aggregation in vitro and HD phenotypes in animal models. However, the role of helicity within N17 on the modulation of polyQ aggregation remains unresolved. Here, we focus on understanding the synergy between the intrinsic helicity within N17 and polyQ length on htt aggregation mechanisms. Through the use of atomistic Monte Carlo simulations utilizing the ABSINTH implicit solvation model, we examine the monomeric properties of N17 permutants with varying degrees of intrinsic helicity as a function of polyQ length. Results suggest that the degree of coupling between N17 constructs and polyQ is dependent on the intrinsic helicity within N17 constructs. A comparative analysis of N17 constructs in cis with a range of polyQ lengths will be combined with biophysical experiments to understand how monomeric properties of N17 modulate the solubility and mechanism of polyQ aggregation.

2442-Pos Board B134
Correlation of Helical Propensity in Amylin Sequences with Known Aggregation Propensity
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Islet amyloid polypeptide (IAPP) is a 37 amino acid peptide and a variety of mutants with different aggregation propensities have been characterized experimentally. Amyloid fiber formation of human IAPP (hIAPP) is toxic to beta-cells of pancreas and associated with type II diabetes. However, rat IAPP (rIAPP), which differs from hIAPP by six residues, is known not to form amyloid fibrils. Moreover, a naturally-occurring point mutation of hIAPP (S20G) is known to form amyloid more quickly and be linked with early onset of type II diabetes. On the other hand, another point mutation of hIAPP (I26P) was reported to resist and potentially inhibit aggregation of the wild-type hIAPP. A critical question regarding disparate aggregation propensity of various amylin sequences is if such differences originate from secondary structure populated in the monomeric state. It has been suggested based on experimental data that transiently sampled helical structures may play an important role in early stages of aggregation. But such expectations have not been directly verified as obtaining residue-specific experimental data on largely disordered proteins is quite challenging. Here, we have studied various IAPP monomers in solution by replica exchange molecular dynamics simulation and an optimized fully atomistic protein force field, Amber03w. We find that alpha-helix propensity in region spanning residues 7 to 16 correlates very well with the known aggregation propensity of these amylin sequences. The peptides with higher alpha-helix stability in this region aggregate more rapidly. Interestingly, all the sequences show very little beta-sheet propensity, which is the dominant secondary structure populated in fibril-like aggregates. Further, we find that the secondary structure adopted in solution by hIAPP is strikingly similar to the NMR structures in presence of micelles. We will discuss the implications of the above observations for the aggregation mechanism.

2443-Pos Board B135
Tau(273-284): A Molecular Dynamics Study of Intrinsically Disordered Protein Conformations in the Presence of Osmolytes
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In contrast to traditional protein structural paradigms, intrinsically disordered proteins (IDPs) represent a unique class of proteins which have very few stable secondary structures. This inherent disorder in native structure allows IDPs to adopt a wide variety of extended and compact conformations upon binding to nearby macromolecules which enable them to perform a large number of vital physiological functions. Here we focus on the microtubule associated tau protein, a classic example of a highly-soluble IDP which helps regulate microtubule growth in the brain. Dysfunctions in tau (i.e. taupathies) are often implicated in Alzheimer's disease and other forms of dementia, as large quantities of tau cross-beta sheets can accumulate and potentially inhibit proper brain function, in additional to deregulating further microtubule growth. Our work builds on our previous studies [1] where we investigated the conformational properties of a fragment of tau which is highly associated with aggregation, specifically the R2/wt tau residues 273-284 (sequence GKVQIINKKLDL). Here we use replica exchange molecular dynamics to study the effect of two important osmolytes, trimethylamine n-oxide (TMAO) and urea, on the folding and aggregation of R2/wt. The overarching goal of our study is aimed at understanding what factors facilitate or inhibit tau aggregation, and identifying (to the extent possible) what physiological factors affect the folding of IDPs since there is still a considerable amount of information to be learned about how these proteins operate in the human body.
[1] L. Larini, M. M. Gessel, N. E. LaPointe, T. D. Do, M. T. Bowers, S. C. Feinstein, and J. E. Shea, "Initiation of assembly of tau(273-284) and its Delta K280 mutant: an experimental and computational study," Physical Chemistry Chemical Physics 15 (23), 8916-8928 (2013).

2444-Pos Board B136
Protein Folding and Collapse: Thermodynamics of Aggregation of Gly_5 vs Concentration in Solution
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Intrinsically disordered proteins (IDPs) are proteins that do not fold into a stable, three-dimensional, structure, and may only undergo ordering when interacting with other molecules. IDPs tend to be rich in amino acids like glycine, which favor the proteins' disorderliness. Hence, oligoglycines are a good model to study the behavior of IDPs in aqueous solvent. Experimentally, the solubility of oligoglycine in water decreases as its length increases until, when the peptide contains 5 glycines, it aggregates and falls out of solution at mM concentration.
We present results of large scale simulations of over 3 million atoms of several hundred short (five residue) oligoglycines at varying concentrations in explicit solvent. We find that intermolecular interactions between oligoglycines are favored over interactions between oligoglycine and water, leading to their aggregation, *viz.* concentration effects play a significant role in driving oligoglycines to aggregate and/or collapse. However, the interaction driving peptide associations, liquid-liquid phase separation, are not predominantly hydrogen bonding. We hypothesize that the thermodynamics of aggregation of short oligoglycines is equivalent to the thermodynamics of collapse of longer oligoglycines and similar disordered domains in water. We compare the aggregation of short oligoglycines with the collapse of longer, single oligoglycines in water.